C. **2,2-Dimethyl-5-(1,2-dibromophenylethyl)-4-oxazolidinone.**—Bromine (3.7 g., 0.023 mole) in 10 ml. of chloroform was added to a solution of 5 g. (0.023 mole) of IIb in 25 ml. of chloroform. The solvent was evaporated and the residue was triturated with ethanol and recrystallized from aqueous ethanol to yield 4.5 g. (52%) of the dibromide, m.p. 182–183° dec.

Anal. Calcd. for $C_{13}H_{15}Br_2NO_2$: Br, 42.39. Found: Br, 42.47.

D. **4-Acetoxy-2,2-dimethyl-5-styryl-3-oxazoline.**—Acetic anhydride (10 ml.) and 1 g. (0.0046 mole) of IIb were refluxed 1 hr. and held at room temperature for 18 hr. Excess acetic anhydride was evaporated *in vacuo*. The residue stirred with cold ethanol yielded 1 g. of crystalline product, m.p. 68–69°. Recrystallization from aqueous ethanol did not raise the melting point. The infrared spectrum corroborated the structure given, having absorption bands at 1320 (–C–O–C–), 1757 (C=O), and 1710 cm.$^{-1}$ (C=N).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.61; N, 5.40. Found: C, 69.47; H, 6.61; N, 5.44.

2,2-Dimethyl-5-phenylsulfonylmethyl-4-oxazolidinone.—A solution of 1 g. (0.004 mole) of 2,2-dimethyl-5-phenylmercaptomethyl-4-oxazolidinone (XIVb) and 2 ml. of 30% aqueous hydrogen peroxide in 5 ml. of acetic acid was heated 1 hr. at 80°. Dilution with 25 ml. of water gave 0.7 g. of product, m.p. 152–153°. Recrystallization from water raised the m.p. to 153–154°.

Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.65; H, 5.52; N, 5.28; S, 12.17.

N,N′-Methylenebis(2-hydroxy-4-phenyl-3-butenamide) (XXX).—A mixture of 10 g. (0.057 mole) of IIa and 100 ml. of chloromethyl methyl ether was refluxed 4 hr. The excess ether was evaporated, and the residue stirred with cold methanol to obtain 1.4 g. of crystalline product, m.p. 216–217°. Two recrystallizations from 2-ethoxyethanol gave small white prisms, m.p. 220–221°.

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65; mol. wt., 366.4. Found: C, 68.93; H, 6.08; N, 7.70; mol. wt., 392.

N,N′-Methylenebis(2-hydroxy-5-phenylvaleramide) was prepared similarly from 2-hydroxy-5-phenylvaleramide (XVIIa) and chloromethyl methyl ether; m.p. 147–148° (from ethanol).

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.33; H, 7.59; N, 7.03; mol. wt., 398. Found: C, 69.68; H, 7.56; N, 7.08; mol. wt., 384.

N-Ethoxymethyl-2-hydroxy-4-phenyl-3-butenamide (XXXI).—A solution of 17.7 g. (0.1 mole) of IIa, 13 g. (0.125 mole) of diethoxymethane, and 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of toluene and 50 ml. of cyclohexane was refluxed 3 hr. with continuous removal of the cyclohexane–ethanol azeotrope as it distilled. The reaction mixture was cooled and the precipitated N,N′-methylenebis(2-hydroxy-4-phenyl-3-butenamide), m.p. 220–221° (3 g.), was filtered off. The filtrate on standing deposited 5 g. of crystals, m.p. 84–85°. Three recrystallizations from benzene–cyclohexane raised the m.p. to 93–94°.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.34; H, 7.28; N, 5.95; mol. wt., 235. Found: C, 65.91; H, 7.08; N, 6.18; mol. wt., 240.

N-Ethoxymethyl-2-hydroxy-5-phenylvaleramide.—A solution of 19.3 g. (0.1 mole) of 2-hydroxy-5-phenylvaleramide (XVII), 13 g. (0.125 mole) of diethoxymethane, and 0.16 g. of *p*-toluenesulfonic acid, in 45 ml. of toluene and 50 ml. of cyclohexane was refluxed 4 hr. with continuous removal of the cyclohexane–ethanol azeotrope. The solution was cooled, filtered, and diluted with an equal volume of petroleum ether to precipitate 7 g. of white crystals, m.p. 62–63°. Recrystallization from cyclohexane did not change the melting point.

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.43; N, 5.58; mol. wt., 251. Found: C, 66.95; H, 8.36; N, 5.77; mol. wt., 255.

N,N′-Methylenebis(2-hydroxy-3,3,3-trichloropropionamide). A solution of 14 g. (0.073 mole) of 2-hydroxy-3,3,3-trichloropropionamide, 11.7 ml. of diethoxymethane, and 0.12 g. of *p*-toluenesulfonic acid, in 35 ml. of toluene and 37 ml. of cyclohexane was refluxed 45 min., with continuous removal of the cyclohexane–ethanol azeotrope. The mixture was cooled, and the crystalline product (4.6 g., m.p. 232–233° dec.) was recrystallized from methanol to obtain 2.5 g. of white needles, m.p. 238–239° dec.

Anal. Calcd. for $C_7H_8Cl_6N_2O_4$: C, 21.18; H, 2.03; Cl, 53.60; N, 7.06; mol. wt., 397. Found: C, 21.24; H, 2.05; Cl, 53.46; N, 7.21; mol. wt., 396.

Acknowledgment.—The authors are indebted to Drs. J. J. Boren and H. M. Hanson for evaluation of the behavioral activity of these compounds.

Behavioral and Neuropharmacological Actions of N-Aralkylhydroxylamines and Their O-Methyl Ethers

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Received June 15, 1964

The syntheses of a number of ring-substituted 1-aryl-2-hydroxyamino- and 1-aryl-2-methoxyaminopropanes are described. These compounds are compared pharmacologically with the corresponding 1-aryl-2-aminopropanes. The hydroxyamino compounds are, in general, central stimulants, and O-methylation diminishes this activity. Two compounds within this series were found to be monamine oxidase inhibitors.

In a continuation of our studies of compounds related to the physiologically active β-phenethylamines,[1] we have synthesized and examined the pharmacology of a number of 4-substituted 1-aryl-2-hydroxyamino- and 1-aryl-2-methoxyaminopropanes (Table I). Substituents which have been examined include methoxy, chloro, methyl, and hydrogen; a few compounds such as 1-(3-indolyl)-2-hydroxyaminopropane and β-1,2,3,4-tetrahydronaphthylhydroxylamine were prepared in order to examine the hydroxyamino analogs of α-methyltryptamine, a monamine oxidase inhibitor, and 1,2,3,4-tetrahydro-β-naphthylamine, a pyretogenic compound which produces rage in the cat.

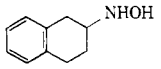
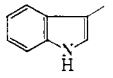
Considerable literature is available on the synthesis and pharmacology of O-substituted aralkylhydroxylamines and related substances.[2] Relatively little work has been reported of the corresponding N-substituted compounds. Major[3] has published a synthesis of 1-

(1) (a) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958); (b) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Am. Chem. Soc.*, **76**, 5555 (1954); (c) *J. Org. Chem.*, **23**, 2034 (1958); (d) *ibid.*, **22**, 332 (1957).

(2) See references at the beginning of E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).

(3) R. T. Major and K. W. Obly, *ibid.*, **4**, 51 (1961).

TABLE I
$ArCH_2CH(CH_3)NX$

Compd.	Ar	X	Formula	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
1	C_6H_5	OH	$(C_9H_{13}NO)_2 \cdot C_2H_2O_4$	174–175[a]						
2	4-$CH_3OC_6H_4$	OH	$(C_{10}H_{15}NO_2)_2 \cdot C_2H_2O_4$	134–135	58.4	58.6	7.1	7.1	6.2	6.1
3	3,4-$(CH_3O)_2C_6H_3$	OH	$(C_{11}H_{17}NO_3)_2 \cdot C_2H_2O_4$	135–136	56.2	56.1	7.0	7.0	5.5	5.5
4	4-ClC_6H_4	OH	$(C_9H_{12}ClNO)_2 \cdot C_2H_4O_4$	192–193	52.0	52.0	5.6	5.4	6.1	6.0
5	4-$CH_3C_6H_4$	OH	$(C_{10}H_{15}NO)_2 \cdot C_2H_2O_4$	186–187	62.8	63.1	7.6	7.5	6.7	6.5
			$(C_{10}H_{13}NO)_2 \cdot C_2H_2O_4$	183–184	63.4	63.3	6.7	6.8	6.7	6.7
6		OH	$C_{12}H_{14}N_2O \cdot C_2H_2O_4$[b]	180–181	57.6	57.8	5.5	5.7	9.6	9.8
7										
8	C_6H_5	OCH_3	$(C_{10}H_{15}NO)_2 \cdot C_2H_2O_4$	129–130	62.9	63.0	7.6	7.7	6.7	6.8
9	4-$CH_3OC_6H_4$	OCH_3	$(C_{11}H_{17}NO_2)_2 \cdot C_2H_2O_4$	129–130	60.0	60.0	7.5	7.3	5.8	5.7
10	3,4-$(CH_3O)_2C_6H_3$	OCH_3	$(C_{12}H_{19}NO_3)_2 \cdot C_2H_2O_4$	116–117	57.9	57.6	7.4	7.6	5.2	5.3
11	4-ClC_6H_4	OCH_3	$(C_{10}H_{14}ClNO)_2 \cdot C_2H_2O_4$	128–129	54.0	54.3	6.1	6.2	5.7	5.6
12	4-$CH_3C_6H_4$	OCH_3	$(C_{11}H_{17}NO)_2 \cdot C_2H_2O_4$	134–135	64.3	64.2	8.0	7.8	6.2	6.0
13	C_6H_5	H	[c]							
14	4-$CH_3OC_6H_4$	H	[c]							
15	4-ClC_6H_4	H	$C_9H_{12}ClN \cdot HCl$	163–165[d]						
16	4-$CH_3C_6H_4$	H	$C_{10}H_{15}N \cdot HCl$[e]	158–159						

[a] Lit.[4] 175–176°. [b] Acid oxalate. [c] Aldrich Chemical Co., Milwaukee, Wis. [d] H. B. Hass [*J. Am. Chem. Soc.*, **68**, 1009 (1946)] reported 164–165°. [e] H. D. Moed, J. van Dijk, and H. Niewind, *Rec. trav. chim.*, **74**, 919 (1955).

phenyl-2-methoxyaminopropane (**8**) and has pointed out the amphetamine-like activity of this compound. We concur with this observation, but our data show this substance to be roughly six times as toxic as the reported figure. Our data on the monamine oxidase inhibitory action of **8**, using tyramine as a substrate, are generally in agreement with Major's observation that this substance shows little or no inhibition of monamine oxidase using 5-hydroxytryptamine as a substrate.

The N-aralkylhydroxylamines and the corresponding O-methyl ethers were synthesized by the following sequence of reactions. Ar was either phenyl or sub-

$$ArCH_2COCH_3 \longrightarrow ArCH_2C(CH_3)=NOR \longrightarrow ArCH_2CH(CH_3)NHOR$$

stituted phenyl, 1,2,3,4-tetrahydronaphthyl, or 3-indolyl. R was H for the hydroxylamines and CH_3 for the O-methyl ethers. The oximes were reduced to hydroxylamines by catalytic hydrogenation over a platinum catalyst in the presence of 1 equiv. of HCl, similar to the procedure of Vavon and Crajeinovic.[4] The corresponding O-methyl ethers were obtained by catalytic reduction of the O-methyl oximes by the method of Jones and Major.[5] The 1-aryl-2-propanones required as starting materials were procured commercially or synthesized by published procedures. All of the aralkylhydroxylamines and the O-methyl ethers were converted to their neutral oxalates for purification and storage.

dl-1-(4-Chlorophenyl)-2-aminopropane (**15**) and *dl*-1-(4-tolyl)-2-aminopropane (**16**) were prepared by reduction of the corresponding substituted 1-aryl-2-nitro-1-propenes with lithium aluminum hydride. All amphetamines were converted to the hydrochloride salts for use.

Pharmacological Methods. Toxicity Experiments.—Groups of 5 mice (Swiss white, random-bred, 25–35 g.) were injected intraperitoneally with aqueous solutions of the hydrochloride salts of the test compounds[6] at a minimum of 4 dose levels spaced in geometric progression between completely killing and living doses. The LD_{50} was estimated by the method of Weil.[7]

Spontaneous Motor Activity (SMA).—Of the various techniques available for the measurement of SMA,[8] it was decided to use the photocell-cage technique on groups of 3 mice/trial to determine the dose necessary to produce a doubling of the motor activity (ED_{200}), based upon the number of interruptions of the light beam compared with saline as the control for standard time periods after i.p. injection.

Hexobarbital Sleep Time.—Adult, male mice in groups of 15 were injected intraperitoneally with 10 mg./kg. of the test compound, and after 15 min. hexobarbital sodium was injected intraperitoneally at a dose of 100 mg./kg. The time between loss and regain of the righting reflex was taken as the duration of sleeping times, which were compared with control sleeping times with hexobarbital alone. The statistical significance of the results was tested by means of the Student t-test.

Relative Pressor Effect.—Effect of the test compounds on blood pressure was measured in a heparinized cat preparation under pentobarbital anesthesia. Drugs were administered intravenously through a jugular cannula, and the change in the mean systolic pressure was measured by means of a Buffington universal pulse transducer oriented dorsally on the tail.[9] Blood pressure effects were compared with the rise obtained with a standard dose (0.1 mg.) of phenethylamine

(4) G. Vavon and M. Crajeinovic, *Bull. soc. chim. Belges*, [4] **43**, 231 (1928).
(5) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, **52**, 669 (1930).

(6) It was noted early in this study that solutions of the hydrochloride salts of these bases undergo gradual decomposition in aqueous solution even at refrigerator temperature. Hence, all compounds were stored as the oxalate salts, and solutions of the hydrochlorides were freshly prepared from the oxalates by treatment with an equivalent amount of $CaCl_2$ and removal of the insoluble calcium oxalate by filtration.
(7) C. S. Weil, *Biometrics*, **8**, 249 (1952).
(8) P. B. Dews and W. H. Morse, *Ann. Rev. Pharmacol.*, **1**, 145 (1961).
(9) F. B. Byrom and C. Wilson, *J. Physiol.* (London), **93**, 301 (1938).

TABLE II

PHARMACOLOGY

Compd.	SMA ED_{200}, mg./kg.	Relative pressor effect (phenethylamine = 1)	LD_{50}, mg./kg.	Effect on hexobarbital sleeping time, % change	Change in rectal temp., °C.	Effect on cat behavior	Monamine oxidase inhibition, %
1	20	1.3	80	−20[a]	+0.6	+	69
2	NA	0.5	100	−5[a]	+2.9	+	47
3	NA	0.3	120	−15[a]	0	—	0
4	5	0.2	10	−50[b]	+4.2	+	
5	20	0.9	8	+15[a]	+2.8	+	
6	50	0.6	50	+115[b]	+1.8	−	87
7	10	0.2	10	+60[b]	+2.5	+	[c]
8	NA	0.1	100	+45[d]	0	−	[c]
9	NA	0.0	200	+50[d]	0	−	[c]
10	NA	0.0	200	+80[b]	0	−	
11	50	0.1	100	+115[b]	0	−	
12	NA	0.0	50	+120[b]	0	−	
13	10	0.8	40	−15[e]	+1.9	+	54
14	10	1.0	40	−15[a]	+3.9	+	[c]
15	5	1.1	15	−45[e]	+4.4	+	42
16	5	0.7	12	−45[e]	+3.9	+	[c]

[a] Not statistically significant. [b] P (statistical probability) < 0.001. [c] No significant inhibition. [d] $P < 0.02$. [e] $P < 0.01$.

and calculated as the pressor effect relative to the effect of phenethylamine = 1.

Cat Behavior Tests.—Gross behavior effects on normal, healthy, adult cats of both sexes injected i.m. with 25 mg./kg. of the test compounds were observed. The behavioral components of aggressive behavior, withdrawal, hiss, growl, pupil dilation, pilomotor effect, and salivation were used as indices to the overall behavioral patterns of the animals as discussed by Norton and de Beer.[10] Rectal temperatures were measured with a Thermistor probe.[11]

Monamine Oxidase (MAO).—Inhibition of this enzyme was determined by comparing the extent of deamination of tyramine (5×10^{-3} M) as a substrate[12] by a solubilized MAO preparation[13] from rabbit liver in the absence and presence of the test compounds at 5×10^{-3} M.

Results

The results of the above pharmacological measurements are summarized in Table II.

Relative Pressor Action.—Pressor data are presented relative to phenethylamine as a unitary standard. With the exception of **1**, **14**, and **15**, all of the compounds tabulated exhibited less pressor activity than the standard. All of the compounds examined gave a prompt increase in blood pressure which returned to the control base-line systolic pressure within about 10 min. after drug administration.

Spontaneous Motor Activity.—Six out of the sixteen compounds examined did not show a significant change in activity (NA) in this experimental design. Most of the compounds which caused significant changes in motor activity were equal or less potent than 2-amino-1-phenylpropane (**13**); 1-(4-chlorophenyl)-2-substituted propanes (**4**, **11**, and **15**) were notable exceptions, in that this subgroup showed a higher SMA than any of the corresponding unsubstituted compounds.

In general, it was found that all of the substituted 2-amino-1-phenylpropanes and their hydroxyamino analogs are rapidly acting, whereas the corresponding methoxyamino compounds exhibit no pronounced excitatory effect immediately after administration to either mice or cats. However, some hours after injection of **8** at a toxic dose level, mice became hyperactive; clonic convulsions and death followed.

Hexobarbital Sleeping Time.—Under the conditions of testing, the 1-aryl-2-hydroxyaminopropanes (**1**, **2**, and **3**) did not change significantly the sleeping time, whereas 1-(4-chlorophenyl)-2-hydroxyaminopropane (**4**) produced inhibition. Of the 1-aryl-2-aminopropanes examined, only **15** and **16** caused the expected inhibition at a relatively high level of significance. All of the substituted 1-aryl-2-methoxyamines (**8** to **12**) were found to potentiate hexobarbital sleeping time.

Cat Behavior.—Compounds which produced a positive reponse in all of the Norton and de Beer parameters at a dose level of 25 mg./kg. (i.m.) were considered to be rage producing. Within this category are all of the ring-substituted 1-aryl-2-aminopropanes (**13**–**16**) and three of the 1-aryl-2-hydroxyaminopropanes. It was of interest to note that those compounds producing a positive rage response correlate well with a general decrease in hexobarbital sleeping time which could be a characteristic of central excitatory action. Notable exceptions to this trend are 1-(3,4-dimethoxyphenyl)-2-hydroxylaminopropane (**3**) and 1-(3-indolyl)-2-hydroxyaminopropane (**7**); **3** has no significant influence on hexobarbital sleeping time and does not induce rage-like behavior in the cat, whereas **7** is the only member of this group which both potentiates sleeping time and produces rage. All strong rage producing compounds were found to cause a moderate to large increase in body temperature.

Compound **1** (25 mg./kg.) evokes a qualitatively lower level of rage response than does 2-amino-1-phenylpropane, but the effects are longer lasting. Animals receiving this compound exhibit an unusual circular head motion accompanied by profuse salivation. Pretreatment of the animals with chlorpromazine (10 mg./kg.) causes a blockade of the rage reaction

(10) S. Norton and E. J. de Beer, *Ann. N. Y. Acad. Sci.*, **65**, 249 (1956).
(11) Yellow Springs Instrument Co. Telethermometer.
(12) R. E. Logsdon, *Ann. N. Y. Acad. Sci.*, **87**, 801 (1960).
(13) G. C. Cotzias, I. Serlin, and J. J. Greenough, *Science*, **120**, 144 (1954).

without inhibiting the head motion[14]; atropine sulfate administration failed to block salivation.

Monamine Oxidase Inhibition (*in vitro*).—The results of these inhibition studies are tabulated in the last column of Table II. 1-(3-Indolyl)-2-hydroxylaminopropane (**7**) caused no significant inhibition of monamine oxidase while 1-(3-indolyl)-2-aminopropane is a potent inhibitor of this enzyme.[15] Compound **1** is moderately active and is an hydroxyamino analog of the well-known MAO inhibitor 2-hydrazino-1-phenylpropane. The most strongly inhibiting substance within the group examined is β-1,2,3,4-tetrahydronaphthylhydroxylamine (**6**) which differs pharmacologically from 1,2,3,4-tetrahydro-β-naphthylamine in that the latter compound is not a MAO inhibitor, is strongly pyretogenic, and induces rage in the cat.[16] Methyl-2-propynylbenzylamine, clearly established as a MAO inhibitor, effected a pronounced inhibition of the enzyme system at a concentration of 5×10^{-3} *M*. In repeated experiments under controlled conditions, a typical level of inhibition was 81–82%.

Structure–Activity Relationships.—Replacement of amino by hydroxyamino in the amphetamine structure decreases but does not abolish the central nervous stimulation effects of this group of compounds. However, when the hydroxy group is methylated to the corresponding methoxyamino derivative, the stimulating effects are abolished and this group of compounds tends to produce central nervous system depression, as evidenced by their potentiating effects on hexobarbital sleeping time in mice.

Hydroxyamino compounds in which the aryl group was not phenyl or substituted phenyl exhibited some anomalous effects. The cyclic analog **6** is a depressant and does not induce a rage response in the cat, yet the hyperthermic effect remains. Substitution of 3-indolyl for phenyl potentiates hexobarbital sleeping time, yet induces a hyperthermia and excitation in the cat.

As was found with phenethylamines,[15a] introduction of methoxy, chloro, or methyl into the 4-position of the benzene ring intensifies the excitant and CNS stimulant effects of both substituted amphetamines and aralkylhydroxylamines. Substitution of more than one methoxy group on the aromatic nucleus, as in **3**, abolishes the excitant activity of this class of compounds.

O-Methylation of the aralkylhydroxylamines profoundly alters the pharmacological activity of these substances. The O-methyl ethers are significantly less toxic, do not induce excited behavior in the cat, and appear to be CNS depressants rather than stimulants in their primary action. The delayed response observed with **8** may indicate that the O-methyl ether is cleaved enzymatically to the active compound **1**.

Experimental[17]

dl-**1-(4-Methoxyphenyl)-2-hydroxyaminopropane** (**2**).—1-(4-Methoxyphenyl)-2-propanone, b.p. 82–85° (0.1 mm.) [lit.[18] 102–105° (0.5 mm.)], was obtained in 86% yield by reduction of 1-(4-methoxyphenyl)-2-nitro-1-propene with iron and hydrochloric acid.[19] This ketone was converted to its oxime[20] in 97% yield by reaction with hydroxylamine hydrochloride and sodium carbonate in an aqueous system at room temperature; m.p. 50–51° (lit.[20] 56–61°). A solution of 35.8 g. of 1-(4-methoxyphenyl)-2-propanone oxime in 250 ml. of 80% ethanol containing 7.3 g. of HCl was hydrogenated for 3 hr. in a Parr hydrogenation apparatus at 3.5 kg./cm.^{2} (50 p.s.i.g.) over 0.5 g. of platinum oxide catalyst The catalyst was removed by filtration, the filtrate was diluted to 1 l. with water and extracted twice with ether to remove any acid-insoluble material. The aqueous layer was made alkaline with solid $NaHCO_3$ (to pH 8–9), and the basic oil which separated was extracted with two 300-ml. portions of ether. The ether solution was dried ($MgSO_4$) and filtered, and the ether was removed by evaporation. The residual crude product solidified; yield, 27.5 g. (76%); m.p. 54–55°. To an ether solution of this base was added a solution of 9.6 g. of oxalic acid dihydrate in a small volume of methanol. The oxalate salt of **2** which separated solidified gradually; it was collected and recrystallized from methanol; yield, 31.2 g. (69%); m.p. 134–135°.

dl-**1-(4-Methoxyphenyl)-2-methoxyaminopropane** (**9**).—To a stirred mixture of 33.5 g. of 1-(4-methoxyphenyl)-2-propanone, 21.7 g. of methoxyamine hydrochloride, and 40 ml. of water was added gradually a solution of 13.8 g. of sodium carbonate in 25 ml. of water at about 10°. The mixture was then stirred at room temperature for 14 hr., and the oily product layer was extracted with ether, dried ($MgSO_4$), and distilled; b.p. 79–80° (0.4 mm.); yield, 34.3 g. (87%) of a colorless oil.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.3. Found: C, 68.6; H, 7.6; N, 7.2.

A mixture of 19.3 g. of the O-methyl ketoxime, 200 ml. of 80% ethanol, 3.7 g. of HCl, and 0.4 g. of platinum oxide was hydrogenated in a Parr apparatus at 3.5 kg./cm.^{2} (50 p.s.i.g.) until 1 mole of hydrogen/mole of compound was absorbed (1 hr.). The catalyst was removed by filtration, and the product was recovered and converted to the neutral oxalate as previously described. The oxalate was recrystallized from methanol–ether; m.p. 129–130°; yield, 13.5 g. (54%).

dl-**1-(3,4-Dimethoxyphenyl)-2-hydroxyaminopropane** (**3**).—1-(3,4-Dimethoxyphenyl)-2-propanone, b.p. 135–140° (0.5 mm.) [lit.[19] 129–133° (0.4 mm.)], was prepared in 78% yield by the procedure described by Shepard, *et al.*[19] The oxime[21] of this ketone, obtained in 83% yield, was an oil, b.p. 140–141° (0.3 mm.). The oxime (31 g.) was reduced by catalytic hydrogenation in exactly the same manner as described previously, and the hydroxyamino compound was converted to the neutral oxalate and recrystallized from methanol–ether; yield, 12.5 g. (33%); m.p. 135–136°.

dl-**1-(3,4-Dimethoxyphenyl)-2-methoxylaminopropane** (**10**).—Treatment of 33.5 g. of 1-(3,4-dimethoxyphenyl)-2-propanone with methoxyamine as described previously gave 34.4 g. (91%) of 1-(3,4-dimethoxyphenyl)-2-propanone oxime O-methyl ether, b.p. 111–113° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.6; N, 6.4. Found: C, 64.3; H, 7.7; N, 6.2.

Catalytic hydrogenation of this compound by the procedure described afforded the oxalate of **10** in 41% yield; m.p. 116–117°.

dl-**1-(4-Chlorophenyl)-2-hydroxyaminopropane** (**4**).—1-(4-Chlorophenyl)-2-propanone, b.p. 75–79° (0.3 mm.), was prepared by the method of Overberger and Biletch.[22] The oxime of this ketone was a colorless, viscous oil, b.p. 111–113° (0.7 mm.), obtained in 92% yield.

Anal. Calcd. for $C_9H_{10}ClNO$: C, 58.8; H, 5.5; N, 7.6. Found: C, 58.9; H, 5.4; N, 7.4.

Catalytic hydrogenation in the same manner described previously afforded **4** in 78% yield.

dl-**1-(4-Chlorophenyl)-2-methoxyaminopropane** (**11**).—Treatment of 20.5 g. of 1-(4-chlorophenyl)-2-propanone with

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methoxyamine gave 22.8 g. (95%) of the oxime O-methyl ether, b.p. 70–75° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.8; H, 6.1; N, 7.1. Found: C, 61.0; H, 6.2; N, 6.9.

Catalytic hydrogenation of this compound gave **11** in 29% yield.

***dl*-1-(4-Methylphenyl)-2-hydroxyaminopropane (5).**—1-*p*-Tolyl-2-propanone,[23] b.p. 62–67° (0.5 mm.) [lit.[23] 92–94° (3 mm.)], was obtained in 79% yield by reduction of 1-*p*-tolyl-2-nitro-1-propene[24] with iron and HCl.

The oxime of this ketone, m.p. 84–85° (lit.[23] 88–89°), was obtained in 87% yield. Catalytic hydrogenation gave **5** in 74% yield.

***dl*-1-(4-Methylphenyl)-2-methoxyaminopropane (12).**—1-*p*-Tolyl-2-propanone oxime O-methyl ether was an oil, b.p. 82–84° (1.3 mm.), obtained in 95% yield by treatment of 1-*p*-tolyl-2-propanone with methoxyamine.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.3; H, 8.2; N, 7.7.

Catalytic hydrogenation afforded **12** in 42% yield.

***dl*-N-[β-(1,2,3,4-Tetrahydronaphthyl)]hydroxylamine (6).**—β-Tetralone oxime[25] (8.6 g.) in 150 ml. of ethanol containing 1.8 g. of HCl was hydrogenated over 0.25 g. of platinum oxide catalyst at 3.5 kg./cm.^{2} (50 p.s.i.g.) until 1 mole equiv. of hydrogen was absorbed. The reaction mixture was processed as described previously, and **6** was isolated as the oxalate, m.p. 183–184°; yield, 3.4 g. (30%).

***dl*-1-(3-Indolyl)-2-hydroxyaminopropane (7).** Crude 1-(3-indolyl)-2-propanone oxime (8 g.), obtained from 3-indoleacetone[26] and hydroxylamine, in 200 ml. of ethanol containing 1.6 g. of HCl was hydrogenated over 0.2 g. of platinum oxide catalyst at 3.5 kg./cm.^{2} (50 p.s.i.g.) until 1 mole equiv. of hydrogen was absorbed. The hydroxyamino compound **7** was isolated as the oxalate, m.p. 180–181°.

***dl*-1-(4-Chlorophenyl)-2-aminopropane (15).**—To a cooled and stirred mixture of 23 g. of lithium aluminum hydride and 500 ml. of anhydrous ether was added gradually a solution of 29.6 g. of 1-(*p*-chlorophenyl)-2-nitro-1-propene[27] in 100 ml. of dry reagent benzene. The reaction mixture was stirred and heated under reflux for 1 hr., cooled, and decomposed with ice water. After filtration from inorganic material, the dried solution was treated with HCl gas to precipitate **15** as the hydrochloride; yield, 25.7 g. (83%); m.p. 163–165°, after recrystallization from ethanol–ethyl acetate–ether.

***dl*-1-(4-Tolyl)-2-aminopropane (16).**—Reduction of 23 g. of 1-(*p*-tolyl)-2-nitro-1-propene with 17 g. of lithium aluminum hydride gave 16.7 g. (70%) of **16** as the hydrochloride, m.p. 158–159°, after recrystallization from ethanol–ethyl acetate–ether.

Acknowledgment.—The authors are indebted to Miss Madeline Winters for her assistance with animal experiments and enzyme inhibition studies. This investigation was supported by Public Health Service Research Grants MH-07842 and HE-06353, from the National Institutes of Health.

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Synthesis and Pharmacological Study of New Piperazine Derivatives. II. Phenethylpiperazines

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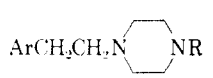
Received May 14, 1964

Thirty-eight 1,4-disubstituted piperazines have been prepared, in which the 1-substituents are phenethyl or its mono- or dimethoxy derivatives, and the 4-substituents are phenyl, mono-, or polysubstituted phenyl, pyridyl, methylpyrazinyl, chloro-, or methoxypyridazinyl. They have been studied systematically for potency against epinephrine and histamine on the isolated guinea pig seminal vesicle, in comparison with ergotamine and promethazine.

In the preceding paper of this series[1] the synthesis and the adrenolytic and antihistaminic activities of a number of benzylpiperazines have been described. We now wish to report the study of phenethylpiperazines of type I, where Ar = phenyl, mono- or dimethoxyphenyl, and R = phenyl, mono-, or polysubstituted phenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl.



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Although a variety of 1,4-disubstituted piperazines are known, only some derivatives of the same general formula have been described specifically.[2]

Phenethylpiperazine derivatives (Table I) were prepared by condensation of the relevant monosubstituted piperazine with the appropriate phenethylhalide in the presence of a twofold excess of the piperazine in xylene (methods A and B) or in the presence of anhydrous potassium carbonate in butanol (method C). The aminophenylpiperazine derivative was obtained

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